Proposed Decision Memo for Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting (CAG-00085R6)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) proposes to make no changes to the national coverage determination (NCD) for percutaneous transluminal angioplasty (PTA) of the carotid artery concurrent with stenting (Medicare NCD Manual 20.7).

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

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SUBJECT: Proposed Coverage Decision Memorandum for Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting

DATE: July 31, 2008

I. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes to make no changes to the national coverage determination (NCD) for percutaneous transluminal angioplasty (PTA) of the carotid artery concurrent with stenting (Medicare NCD Manual 20.7).

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

II. Background

Every year about 780,000 people in the United States experience new or recurrent stroke. About 600,000 are first attacks and 180,000 are recurrent attacks (Rosamond et al., 2008). The term stroke refers to a "group of cerebrovascular disorders in which part of the brain is transiently or permanently affected by ischemic or hemorrhage, or in which one or more blood vessels of the brain are primarily affected by a pathologic process, or both" (Topol, 2002). Of all strokes 87% are ischemic, 10% are intracerebral hemorrhage and 3% are subarachnoid hemorrhage (Rosamond et al., 2008).

Although carotid artery stenosis is an important predictor for stroke, it has been estimated that 20% and 45% of all strokes in patients with 70-99% carotid stenosis are unrelated to the carotid disease (Barnett, 2000). In patients whose stroke is not due to carotid artery disease, aggressive medical therapy would be the most important treatment since surgical intervention would not reduce these strokes.

Treatment strategies for atherosclerotic carotid stenosis include aggressive medical therapy, carotid endarterectomy (CEA) and carotid artery stenting (CAS). Aggressive medical therapy may involve the utilization of anti-platelet agents, statins, antihypertensives, anti-ischemic perioperative beta blockers, risk factor modification (including smoking cessation and diabetic control) plus lifestyle modification (exercise).

CEA is a surgical procedure used to prevent stroke in which a surgeon removes fatty deposits or ulcerated and stenotic plaques from the carotid arteries, the two main arteries in the neck supplying blood to the brain.

CAS is performed with a catheter, usually inserted through the femoral artery, and threaded up to the carotid artery beyond the area of narrowing. A distal embolic protection device or filter is usually placed first to catch emboli or debris that may dislodge during the procedure. A self-expandable or balloon-expandable, metal mesh stent is then placed to widen the stenosis and the protection device is removed.

For patients with carotid artery stenosis, the decision to treat with CEA or CAS may be influenced by anatomical factors. Certain anatomical lesions may place patients at high risk for CEA while other lesions may make CAS much more risky.

On December 14, 2007, CMS received a joint request from the American College of Cardiology (ACC), the Society for Cardiovascular Angiography and Interventions (SCAI), the Society of Vascular and Interventional Neurology (SVIN) and the Society for Vascular Medicine (SVM) to revise current Medicare policy to extend coverage to “patients who are at high risk for carotid endarterectomy (CEA) due to defined anatomic factors, and who have either symptomatic carotid artery stenosis of 50 - 69% (or greater) or asymptomatic carotid artery stenosis of ≥ 80%.” The requestors define anatomic factors as:

- Previous CEA with recurrent stenosis,
- Prior radiation therapy to neck,
- Previous ablative neck surgery (e.g., radical neck dissection, laryngectomy),
- Surgically inaccessible carotid lesion located above cervical vertebra C2,
- Common carotid artery lesion below the clavicle,
- Contralateral vocal cord palsy,
- Presence of tracheostomy stoma,
- Contralateral internal carotid artery occlusion,
- Immobile neck, and
- Severe tandem lesions.

The requestors stated that “There is compelling clinical rationale and need for patients in the anatomic group defined above to have access to CAS. These patients do not have an acceptable surgical option, due to their anatomic conditions, which inherently preclude or severely limit safe surgical access.” They also “recommend that CMS’s new coverage policy mandate participation in robust data registries such as NCDR’s CARE registry (see: http://www.accncdr.com/webncdr/CarotidStent/Default.aspx). High quality audited data generated by such registries will help CMS assess the wisdom of our requested coverage expansion and may provide some guidance for future decisions regarding coverage.”

III. History of Medicare Coverage

Over the past seven years, Medicare has expanded coverage for PTA and stenting of the carotid artery. Medicare first covered PTA of the carotid artery concurrent with stent placement in accordance with the Food and Drug Administration (FDA) approved protocols governing Category B Investigational Device Exemption (IDE) clinical trials and later in FDA required post approval studies (Medicare NCD Manual 20.7B2, B3).

Effective March 17, 2005, Medicare expanded coverage for PTA and stenting of the carotid artery when performed on patients at high risk for CEA who also have symptomatic carotid artery stenosis $\geq$ 70% only when performed in a CMS approved facility for CAS with FDA-approved carotid artery stenting systems and embolic protection devices. Symptoms of carotid artery stenosis include carotid transient ischemic attack (TIA) (distal focal neurological dysfunction persisting less than 24 hours), non-disabling stroke (Modified Rankin Scale score < 3 with symptoms for 24 hours or more), and transient monocular blindness (amaurosis fugax) (Medicare NCD Manual 20.7B4).

Effective April 30, 2007, Medicare maintained the existing coverage policy and included detailed facility recertification instructions in the NCD.

Medicare's NCD for PTA concurrent with carotid stenting can be found in NCD Manual 20.7. Medicare's NCD for PTA concurrent with carotid stenting in FDA approved post approval studies can also be found in NCD Manual 20.7B3.

Benefit Category Determination

For an item or service to be covered by the Medicare program, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act. PTA of the carotid artery concurrent with stenting, at a minimum, falls under the benefit categories set forth in section §1861(b) (inpatient hospital services), a part A benefit under §1812(a)(1) and §1861(s)(1) (physician services), a part B benefit. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

February 1, 2008	CMS accepted formal request and initiated review.
March 2, 2008	Initial 30-day public comment period closed.
June 11, 2008	CMS received an additional request to "consider a requirement that the national society registries serve as the CAS outcomes reporting mechanism, with simultaneous discontinuation of the current CMS CD-based data submission system."
July 31, 2008	Proposed decision memorandum posted; 30-day comment period begins.

V. FDA Status

There are currently six carotid stent systems with Premarket Approval (PMA) approval by the FDA plus five distal filter embolic protection devices (EPDs) and one distal balloon occlusion with FDA 510(k) clearance available for use in the common and internal carotid arteries.

VI. General Methodological Principles

When making national coverage decisions, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

This section summarizes the evidence evaluating CAS for patients with symptomatic or asymptomatic carotid stenosis who exhibit “anatomic factors” potentially placing them at high surgical risk for CEA. It incorporates all evidence from prior decision memoranda regarding this issue. A summary of the body of evidence reviewed to date in developing this proposed decision memorandum is available via the final decision memoranda released following the completion of each of the prior national coverage analyses (NCAs) for reconsiderations of the CAS national coverage determination. Although older age (> 80 years) is not an anatomical factor, a commenter suggested coverage modifications in this group, so we also reviewed new articles that addressed this population.

Our present discussion of evidence reviewed focuses upon whether the body of evidence is sufficient to draw conclusions about health outcomes for CAS, as well as whether the available evidence is generalizable to Medicare patients. As in our prior reviews of CAS, the key outcomes of interest to CMS are the periprocedural (occurring during procedure or up to 30 days after) and long-term risk of stroke and death following CAS.

As in the reconsideration of this topic issued April 30, 2007, we will apply the professional society guidance that the accepted standards for carotid revascularization should apply to CAS if it is to be considered an alternative to CEA. Professional guidelines developed and published by the American Heart Association (AHA) (Sacco, et al., 2006; Goldstein et al., 2006) identify these benchmarks and establish that CEA is indicated in patients with asymptomatic and symptomatic carotid artery stenosis when surgeons can achieve perioperative morbidity and mortality rates that are < 3% and < 6% respectively. Similar periprocedural rates are required to consider that CAS improves health outcomes.

This NCA is focused on the anatomical factors that would make CEA relatively or explicitly contraindicated and for which CAS could be an alternative. While we will not discuss those circumstances where CAS is contraindicated, we encourage the stenting community to be very cognizant of the limitations of CAS and to consider these and other factors when selecting patients for the procedure.

Questions

CMS analyzed the following questions for this decision memorandum:

- *Is the evidence sufficient to conclude that defined anatomic factors can be identified among patients with carotid stenosis that make CEA contraindicated?*
- *Is the evidence sufficient to conclude that PTA with CAS improves health outcomes for patients in whom CEA surgery is contraindicated due to anatomic factors with either (a) symptomatic carotid artery stenosis $\geq$ 50% or (b) asymptomatic carotid artery stenosis $\geq$ 80%?*

B. Discussion of evidence reviewed

1. Literature Search

Because this is a reconsideration, CMS focused on new clinical research studies, technology assessments, guidelines and reviews published since the April 30, 2007 decision memorandum, but also considered literature addressing the patient populations under consideration which was published prior to the 2007 NCD. PubMed was searched and general keywords included carotid, stent, stenting, endarterectomy, revascularization, restenosis, anatomic factors and anatomical characteristics. New studies must have presented original data, examined primary health outcomes and been published in peer-reviewed English language journals. Abstracts were excluded.

CMS reviewed all evidence returned from the PubMed search and identified the relevant literature that specifically examined the patient populations under reconsideration. Those studies and articles that did not provide information specific to these populations and thereby were not assistive in answering the questions identified above are not summarized below. That evidence was not included in developing the proposed decision memorandum.

2. External technology assessments and systematic reviews

Blue Cross Blue Shield, 2007
In June 2007, Blue Cross Blue Shield (BCBS) published a Technology Evaluation Center (TEC) assessment for “Angioplasty and Stenting of the Cervical Carotid Artery with Embolic Protection of the Cerebral Circulation.” In its discussion sections for symptomatic (1C) and asymptomatic patients (2C) at “increased anatomic risk,”[1] BCBS TEC found insufficient evidence but noted for “increased anatomic risk” patients:

> “No study reported outcomes specific to this group. However, in BEACH [Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients], the periprocedural stroke rate in the increased anatomic risk group (symptomatic and asymptomatic) was 3.5% and death/stroke or MI rate was 3.9% [30 day results by White, *et al.* 2006]. While the result is suggestive, the absence of reporting according to the presence of symptoms and being a single registry, precludes conclusions.”[2]

In its summary section, the BCBS Medical Advisory Panel made the following judgments about whether CAS with or without embolic protection device (EPD) met its TEC criteria (i.e., its five standard criteria) to reduce stroke risk from symptomatic or asymptomatic carotid stenosis:

1. "***The technology must have final approval from the appropriate governmental regulatory bodies.*** CAS with or without EPD is a procedure and thus does not require U.S. Food and Drug Administration (FDA) approval. However, the devices used for CAS and for EPD require FDA approval. As of this writing, five manufacturers' stents are FDA approved and indicated specifically for use in carotid arteries. The FDA has mandated postmarketing studies for these devices, including longer follow-up for patients already reported to the FDA, and additional registry studies primarily to compare outcomes as a function of clinician training and facility experience. The devices are indicated for combined use of a stent and EPD to reduce stroke risk in patients at increased risk for perioperative complications from CEA who are symptomatic with $\geq$ 50% stenosis or asymptomatic with $\geq$ 80% stenosis. CAS with these devices for patients outside these indications is an off-label use."

2. "***The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.*** Available evidence permits conclusions regarding periprocedural complication rates (particularly stroke or death) following CAS in patients of average risk and increased medical risk. Periprocedural stroke/death rates surpassed those established as clinically acceptable and associated with an overall net health benefit following CEA. There is limited evidence and a clinical rationale to suggest CAS may be beneficial in the group of patients at increased anatomic risk, but present evidence has not clearly differentiated outcomes for this subgroup according to symptomatic status. Thus, there is insufficient evidence to draw conclusions regarding patients at increased anatomic risk. A number of large ongoing trials will yield more evidence in the near future (e.g., "Carotid Revascularization Endarterectomy versus Stent Trial" [symptomatic and asymptomatic]; "International Carotid Stenting Study" [symptomatic]; and the "Asymptomatic Carotid Surgery Trial" ACT-1)."

3. "***The technology must improve the net health outcome.*** Available evidence does not support concluding that CAS with EPD improves the net health outcome among patients at average or increased medical risk. Evidence regarding patients at increased anatomic risk is suggestive of benefit, but insufficient to draw conclusions."

4. “***The technology must be as beneficial as any established alternatives.*** Available evidence does not support concluding that CAS with or without EPD is as beneficial as CEA for symptomatic patients at average risk or increased medical risk. Whether CAS with EPD is as beneficial as CEA for asymptomatic patients at average medical or anatomic risk cannot be determined because available evidence is insufficient to permit conclusions. There is no evidence comparing best medical therapy for symptomatic or asymptomatic patients at increased medical or anatomic risk, preventing conclusions.”

5. “***The improvement must be attainable outside the investigational settings.*** Whether CAS with EPD improves health outcomes has not yet been demonstrated in the investigational setting.

Based on the above, use of carotid artery angioplasty and stenting with or without embolic protection of the cerebral circulation for patients with carotid artery stenosis does not meet the TEC criteria.”

Cochrane, 2007

In October 2007, Ederle et al. published the latest Cochrane Database of Systematic Review on "Percutaneous Transluminal Angioplasty and Stenting for Carotid Artery Stenosis. The review assessed the benefits and risks of CAS compared with CEA or medical therapy, and searched the Cochrane Stroke Group trials register (last searched 14 March 2007), the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 1, 2007), MEDLINE (1950 to March 2007), EMBASE (1980 to March 2007) and Science Citation Index (1945 to March 2007). It also contacted researchers in the field. Selection criteria included randomised trials of CAS compared with CEA or medical therapy for carotid stenosis. One review author independently applied the inclusion criteria, extracted data and assessed trial quality, and search results were validated by a second review author. For the main results, data were available from 12 trials (3227 patients) but not all contributed to each analysis. The Cochrane group's primary outcome comparison of any stroke or death within 30 days of treatment favored surgery (odds ratio (OR) 1.39, P = 0.02, not significant (NS) in the random-effects model). The following outcome comparisons favored CAS over CEA: cranial neuropathy (OR 0.07, P < 0.01); 30 day neurological complication or death (OR 0.62, P = 0.004, NS in the random-effects model, with significant heterogeneity). The following outcome comparisons showed little difference between CAS and CEA: 30 day stroke, myocardial infarction or death (OR 1.11, P = 0.57 with significant heterogeneity); stroke during long-term follow up (OR 1.00). Comparison between CAS with or without protection device showed no significant difference in 30 day stroke or death (OR 0.77, P = 0.42 with significant heterogeneity). Analysis of stroke or death within 30 days of the procedure in asymptomatic carotid stenosis showed no difference (OR 1.06, P = 0.96). In patients not suitable for surgery, there was no significant difference in 30 day stroke or death (OR 0.39, P = 0.09 with significant heterogeneity). The authors concluded that the data were difficult to interpret because trials were substantially heterogeneous (different patients, endovascular procedures, and duration of follow up) and five trials were stopped early, perhaps leading to an over-estimate of the risks of CAS. The pattern of effects on different outcomes did not support a change in practice away from recommending CEA as treatment of choice for suitable carotid stenosis. Regarding research implications, the 2007 Cochrane review advised that the data support continued enrollment of patients within RCTs evaluating endovascular and surgical interventions, that randomization should continue in ongoing trials, and that facilities not participating in large multicenter trials randomize suitable patients locally (Ederle et al*.,* 2007).

Schnaudigel et al., 2008

In June 2008, Schnaudigel and colleagues reported a systematic analysis of all peer-reviewed studies published between January 1990 and June 2007 describing occurrence of new diffusion-weighted imaging (DWI) lesions after CAS or CEA. In 32 studies comprising 1363 CAS and 754 CEA procedures, results showed incidence of any new DWI lesion was significantly higher after CAS (37%) versus CEA (10%) ($P < 0.01$). Similar results were obtained in a meta-analysis focusing on those studies comparing incidence of new DWI lesions after either CEA or CAS (OR, 6.1; 95% CI, 4.19 to 8.87; $P < 0.01$). Use of cerebral protection devices (33% with versus 45% without; $P < 0.01$), closed-cell designed stents during CAS (31% closed-cell vs 51% with open-cell stents; $P < 0.01$) and selective versus routine shunt use during CEA (6% vs 16%; $P < 0.01$) significantly reduced incidence of new ipsilateral DWI lesions. The authors described that the major risk for both CEA and CAS appeared to be the possibility of periprocedural embolic strokes attributable to release of debris during surgical or endovascular manipulation with distal embolization into the cerebral vasculature. They also described that the higher incidence of new DWI lesions (37% for CAS versus 10% for CEA) pointed to increased risk of periprocedural embolism during CAS largely related to manipulation of catheters, guidewires and sheaths in the supra-aortic vasculature, plus possibly a consequence of diagnostic angiography performed before CAS. Schnaudigel's group concluded that new DWI lesions occur more frequently after CAS than after CEA, and that DWI presently appears to be an ideal tool to compare and improve both interventions (Schnaudigel et al., 2008).

3. Internal technology assessment

CMS found no new comparative studies powered for statistical significance allowing analysis of the requestors' group of "anatomic factors," but CMS did summarize 15 retrospective observational studies and one postmarket registry.

<u>Evidence for use of CAS in patients with anatomical lesions making CEA potentially contraindicated</u>

Friedell et al., 2007

Friedell and colleagues reported a single-center, retrospective review of 44 consecutive patients who underwent 46 CAS procedures, including 34 (74%) carotid stents placed in asymptomatic (asx) patients, which were all performed by one interventional radiologist between February 1999 and July 2003. Arch aortography was performed, followed by carotid and intracranial arteriograms before and after stenting. Two cases each required two stents, and embolic protection devices (EPDs) were notably only used late in the series in three procedures. Mean age was 73 years (range, 56-87 years), including 25 males (57%) and 10 patients (23%) ≥ 80 years old. All patients had ≥ 80% carotid stenosis and were considered anatomically or medically at high-risk for CEA, including 34 patients with prior CEA (28 asx), three irradiated neck (two asx), one prior CEA/irradiated neck (asx), one radical neck dissection (asx), one high lesion (asx) and six medical risk (three asx). Half of the 34 recurrent stenoses occurred < 3 years and half ≥ 3 years after the original CEA. Results showed no deaths at 30 days but one stroke (on day 26) due to an occluded ipsilateral carotid documented arteriographically after the patient became acutely hemiparetic, plus three periprocedural transient ischemic attacks (TIAs) – two occurring with use of EPDs – and an acute MI in one of the TIA patients. Duplex ultrasound scans were performed on 44 of 46 (96%) of patients at mean follow-up of 40 months (range, 2-88 months). Two patients, both of whom had prior irradiation, developed three new 80-99% stenoses requiring three stents. The authors concluded that CAS in a community hospital is durable and can have 30-day stroke/mortality equivalent to CEA. A supplemental discussion section following the conclusion emphasized that 34 of 46 stents had been placed for recurrent stenosis (mostly in asymptomatic patients) and that their findings were not generalizable (Friedell et al., 2007).

Protack et al., 2007

Protack and colleagues examined a prospective database of patients undergoing CAS for significant atherosclerotic occlusive disease (ASOD) and radiotherapy-induced (XRT) occlusive disease. Twenty three (15%) patients were treated with CAS for XRT and 127 (85%) patients were treated with CAS for ASOD. All cause mortality at 30-days was 0% for the XRT group and 1% for the ASOD group (no statistical significance) and overall survival at 3 years was equivalent. As defined in the SAPPHIRE trial, there was no significant difference in major adverse event rates nor was there a significant difference in the 3-year neurologic event free rates (87% for XRT and 85% for ASOD). The XRT group has a significantly worse 3-year freedom from restenosis rate of 20% vs. 74% for the ASOD group ($P < .05$). The XRT group also experienced a significantly worse 3-year patency rate of 91% as compared to 100% for the ASOD group. Based upon these findings, the authors conclude that “CAS is equally effective in preventing recurrent symptoms in XRT patients as in ASOD patients,” although the “XRT patients show increased rates of restenosis, reintervention, and occlusion.” Protack and colleagues conclude that “CAS for radiation arteritis has poor long-term anatomic outcome and can present with late occlusions. These findings suggest that these patients require closer perioperative surveillance and raise the question of whether CAS is appropriate for carotid occlusive lesions caused by radiation arteritis” (Protack et al., 2007).

CASES-PMS, 2007

Katzen and colleagues reported 30 day results for the "*C*arotid *A*rtery *S*tenting with *E*mboli Protection *S*urveillance-*P*ost *M*arketing *S*tudy" (CASES-PMS), which was initiated as a non-randomized, condition of approval study under an FDA investigational device exemption (IDE). This single-arm, industry-sponsored registry study examined whether physicians with varying carotid stent experience would obtain safety and efficacy outcomes as good as those from the pivotal "*S*tenting and *A*ngioplasty with *P*rotection in *P*atients at *Hi*gh *R*isk for *E*ndarterectomy" (SAPPHIRE) (Yadav et al., 2004) trial following participation in a comprehensive carotid stent training program. Patients at high surgical risk who were either symptomatic with ≥ 50% stenosis or asymptomatic with ≥ 80% stenosis of the common or internal carotid artery received CAS with distal emboli protection. Physicians were qualified based on prior experience in CAS or following participation in a formal training program. The primary endpoint of major adverse events (MAE) at 30 days (death, MI, or stroke) was tested for noninferiority compared with an objective performance criterion (OPC) of 6.3% established from the stent cohort of the SAPPHIRE trial. Results showed the 30-day MAE rate was 5.0%, meeting the criteria for noninferiority to the prespecified OPC (95% CI [3.9%, 6.2%] P < 0.001). Asymptomatic patients (N = 1158, 78.2%) had similar outcomes to overall results (MAE 4.7%). Outcomes were similar across levels of physician experience, carotid stent volume, geographic location and presence/absence of training program. The authors concluded that utilizing a comprehensive training program, CAS by operators with differing experience in a variety of practice settings yielded safety and efficacy outcomes similar to those reported in the SAPPHIRE trial (Katzen et al., 2007).

Eskandari et al., 2007

Eskandari and colleagues reported a single-center, retrospective review of 269 CAS procedures performed on 264 patients from May 2001 to July 2006 that included 66 procedures following external-beam neck irradiation (N = 26) or CEA (N = 40). In this "hostile neck" group, 47 of 66 procedures (71%) were for asymptomatic ≥ 80% stenosis. A variety of cerebral protection devices were used in 249 of 269 cases (93%). In the remaining 20 cases, devices were not yet available (15) or were unable to be safely delivered (5). In 37 cases, two stents were used due to target lesion length, tandem (ostial and bifurcation) lesions or stent malpositioning. Results showed no significant difference in the rate of restenosis or occlusion between hostile neck lesions (4.5%, 3 of 66) and the remaining group of de novo atherosclerotic lesions (2.0%, 4 of 203), but multiple patient characteristics (including age, sex, comorbidities, stent and embolic protection device type) exhibited significant differences between the groups. During mean follow-up of 16 ± 14 months (range, 1-70 months), two asymptomatic carotid occlusions were detected and those patients were subsequently managed medically. The other five patients with restenosis, repeat angioplasty with stenting (3 patients) or with angioplasty alone (2 patients) resulted in no periprocedural stroke or death. The authors concluded that early periprocedural CAS outcomes were similar in de novo lesions as in patients with a history of neck irradiation or CEA (Eskandari et al., 2007).

BEACH, 2008

Iyer and colleagues' multicenter, single-arm "*B*oston Scientific *E*PI: *A* *C*arotid Stenting Trial for *H*igh-Risk Surgical Patients" (BEACH) study reported one year outcomes in high surgical risk patients with carotid artery stenosis. This non-randomized, industry-sponsored registry study enrolled 480 "pivotal" patients (i.e., 480 of 747 total patients in the trial and excluding 189 patients from the roll-in group and 78 patients in the bilateral registry group) who were candidates for carotid revascularization but considered high surgical risk due to pre-specified anatomic criteria and/or medical comorbidities. The primary endpoint (all stroke, death, or Q-wave MI through 30 days; non–Q-wave MI through 24 hours; and ipsilateral stroke or neurologic death through one year) was compared with a proportionally weighted OPC of 12.6% for published surgical endarterectomy results in similar patients, plus a pre-specified noninferiority margin of 4%. Results among the pivotal patients showed 41.2% were at high surgical risk due to comorbid risk factors and 58.8% due to anatomic risk factors; 76.7% were asymptomatic with flow-limiting carotid stenosis > 80%. At one year, the composite primary endpoint occurred in 8.9% (40 of 447), with repeat revascularization rate of 4.7%. Within this group, age $\geq$ 75, comorbid risk category, diabetes and symptomatic status were associated with 1-year morbidity and mortality, although the magnitude of the effect was not reported. With an upper 95% confidence limit of 11.5% for the primary composite endpoint, study results met prespecified criteria for noninferiority relative to a calculated OPC plus noninferiority margin (16.6%) for historical surgical CEA outcomes in similar patients ($p < 0.0001$ for noninferiority). The authors concluded that CAS with embolic protection is noninferior to CEA at one year in high surgical risk patients. The BEACH registry study was not powered to show statistical significance for unfavorable anatomical characteristics as defined by either anatomic risk only or both anatomic and comorbid risks or a combination of the two (Iyer et al., 2008).

CABERNET, 2008

Hopkins and colleagues' multicenter, single-arm "*C*arotid *A*rtery Revascularisation Using the *B*oston Scientific *E*PI Filte*r*Wire EX/EZ and the EndoTex *Ne*xSten*t*" (CABERNET) study reported one year outcomes in high surgical risk patients with carotid artery stenosis. This non-randomized, industry-sponsored registry examined 454 patients – 288 (63.4%) with anatomic-only risk factors, 89 (19.6%) with comorbid-only risk factors, and 77 with both anatomic and comorbid risk factors - including 110 patients (24.2%) who were symptomatic at entry with ≥ 50% angiographic carotid stenosis and 344 patients (75.8%) who were asymptomatic at entry with ≥ 60% angiographic carotid stenosis. The study was designed with two primary endpoints: 1) the one year major adverse event (MAE) rate defined as any death, stroke or MI as compared to an OPC of 12.1% plus a prespecified noninferiority margin or "delta" of 4%; and 2) the composite rate of 30-day MAE plus late (31-365 days) ipsilateral stroke. Excluding 16 patients in the denominator, results showed the first primary endpoint – the one year MAE rate – equaled 11.6% (51/438), which was noninferior to the OPC of 12.1% (95% upper CI of 14.5% versus OPC plus delta of 16.1%, P = 0.005). Excluding 30 event-free patients with insufficient follow-up from the denominator, the second primary endpoint – the composite rate of 30-day MAE plus late ipsilateral stroke – was 4.7% (20/424) with a 95% upper CI of 6.8%. At one year there was 4.3% mortality, 5.0% stroke and 4.1% MI; and late ipsilateral stroke was 0.7%. Based on "historical controls," the authors concluded that CAS was noninferior to "traditional CEA" at one year in high surgical risk patients. There were no significant differences in one year outcomes between the anatomic and comorbid high-risk groups. The CABERNET registry study was not powered to show statistical significance for unfavorable anatomical characteristics as defined by either anatomic risk only or both anatomic and comorbid risks or a combination of the two (Hopkins et al., 2008).

<u>Evidence on CAS in patients > 80 years old</u>

Lam et al., 2007

Lam and colleagues retrospectively reviewed the impact of increasing age on anatomic factors and complications in 135 carotid stenting procedures performed in 133 patients, which included 87 (65%) males, 46 (35%) women and 37 (28%) patients > 80 years old. Digital subtraction angiograms for each patient were evaluated by two independent observers blinded to patient identifiers, and anatomic characteristics – including aortic arch elongation, arch calcification, arch vessel origin stenosis, common and internal carotid artery tortuosity, treated lesion stenosis, calcification and length – impacting the performance of CAS were assessed as favorable or unfavorable. Postoperative events were defined as MI, stroke and death. Results showed patients > 80 years old had increased prevalence of unfavorable arch elongation ($P = 0.008$), arch calcification ($P = 0.003$), common carotid or innominate artery origin stenosis ($P = 0.006$), common carotid artery tortuosity ($P = 0.0009$), internal carotid artery tortuosity ($P = 0.019$), and treated lesion stenosis ($P = 0.007$). No significant difference was found for treated lesion calcification or length. Perioperative cerebrovascular accidents occurred in four patients (3.0%; three no residual deficit, one residual deficit), MI in three patients (2.2%), and one death (0.8%) secondary to hemorrhagic stroke. Combined stroke, MI and death rate for the entire study population was 3.7%, which was significantly increased ($P = 0.012$) in patients > 80 years old (10.8%) compared to those < 80 years old (1%). Lam et al. concluded that patients > 80 years had a higher incidence of anatomy increasing technical difficulty of performing CAS and that this increase in unfavorable anatomy might be associated with CAS complications. The authors acknowledged the relatively small number of patients treated and the infrequency of neurologic events limiting their ability to demonstrate statistically significant associations between unfavorable anatomic characteristics and neurologic complications. While additional limitations included the qualitative assessment of arterial anatomic features and that CAS patient selection was not randomized, Lam and colleagues cautioned that the presence of unfavorable anatomy warrants serious consideration during workup of patients being evaluated for carotid stenting (Lam et al., 2007).

Sayeed et al., 2008

Sayeed and colleagues reported on 421 patients who underwent 429 CAS procedures between June 1996 and June 2005 for symptomatic or asymptomatic carotid stenosis who met minimal review criteria for availability of preoperative angiographic data and follow-up records including pre-procedural, intra-procedural and immediate post-procedural evaluation as well as 30 day follow-up visit. Demographic data and procedural variables were recorded, including use of cerebral protection device. Angiograms were reviewed for lesion length, percent stenosis, ostial involvement, ulceration, calcification and occlusion of the contralateral common or internal carotid artery. Neurologists evaluated patients before and ≤ 24 hours after CAS, and periprocedural stroke and 30 day adverse event rates (stroke, MI and death) were recorded. Results showed periprocedural all-stroke rate was 3.7%. Octogenarians had significantly higher incidence of 30 day adverse events (10% versus 3.8%; *P* = 0.029), and patients with lesions ≥15 mm had 17% periprocedural stroke and 19.1% 30 day adverse events. Incidence of periprocedural stroke was significantly increased for lesions ≥ 15 mm (8/47, 17% versus 8/382, 2.1%; *P* < 0.001) and for ostial centered lesions (11/154, 7.1% versus 5/275, 1.8%; *P* = 0.007). Multivariate regression identified lesion length ≥15 mm (OR, 6.38; 95% CI, 35 to 17.29) and ostial involvement (OR, 3.12; 95% CI, 3.12 to 8.36) as independently associated with 30 day stroke rate. Lesion calcification, ulceration, degree of stenosis, and presence of contralateral occlusion were not associated with adverse outcomes. Use of cerebral protection devices studied separately in 241 patients (56%) did not change observed correlations between angiographic characteristics and adverse procedural events. The authors concluded that angiographic characteristics such as long stenotic lesions (≥ 15 mm) and involvement of the internal carotid ostium predicted a higher risk of adverse outcomes, and that the indication for CAS in such patients should be carefully evaluated (Sayeed et al., 2008).

Evidence on CEA with anatomical risk factors

Rouleau et al., 1999

Rouleau and colleagues examined 853 patients who underwent angiogram between January 1994 and June 1996 for carotid occlusive disease. Of these patients, 66 were found to have carotid artery tandem lesions and 48 of these 66 patients underwent CEA. Eight adverse postoperative events occurred in seven of the patients who underwent CEA, which included 3 cerebral infarctions and 2 MIs that were resolved within 90 days, 2 instances of severe cranial nerve palsy persistent beyond 90 days and 1 death due to MI. The authors noted that "It is not apparent that complications occurred at a higher rate in perioperative period in patients undergoing endarterectomy with tandem lesions" and conclude that "The presence of a tandem lesion infrequently alters the surgeon's decision to perform an endarterectomy" (Rouleau et al., 1999).

Rockman et al., 2002

Rockman (2002) conducted a retrospective review of a prospectively compiled computerized database of all primary CEAs performed on 2420 patients between 1985 and 1999 by the Division of Surgery at the New York University Medical Center. The review compared results of CEAs performed in patients with carotid contralateral occlusion (CO) (14%) to results from CEA patients with patent contralateral arteries. The authors found no significant differences in perioperative MI, neurologic deficit and mortality between the two patient groups. In asymptomatic patients, no difference between the groups was seen in the rate of perioperative neurologic events (1.8% for CO cases; 1.9% for non-CO cases). Symptomatic patients also showed no significant difference in the rate of perioperative neurological events (3.7% for CO cases; 2.2% for non-CO cases; P = 0.2). The authors also found no significant difference between asymptomatic and symptomatic cases in perioperative mortality related to CO. Rockman and colleagues concluded that "the presence of a CO does not appear to significantly increase the perioperative risk of CEA…CEA can be performed safely in patients with CO, which should not be considered a high-risk condition for surgery in favor of angioplasty and stenting" (Rockman et al., 2002).

Reed et al., 2003

This retrospective analysis of 1370 CEAs performed from 1990 to 1999 examined the influence of numerous risk factors that often cause patients to be excluded from trials on CEA outcome at Brigham and Women's Hospital. The eight risk factors examined included age > 80, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), renal failure, contralateral carotid artery occlusion, recurrent ipsilateral carotid artery stenosis, ipsilateral hemispheric symptoms within 6 weeks, and recurrent coronary artery bypass graft (CABG). Of the eight risk factors studied, only contralateral occlusion was found to be a predictor of poor outcome (P = 0.01). Five (6.7%) of the 75 patients with contralateral carotid occlusion, had adverse perioperative outcome (1 death, 1 disabling stroke, 3 nondisabling stroke). Patients with contralateral carotid occlusion as compared to patients without contralateral carotid occlusion had significantly diminished survival rates at 2 years (P < 0.046) and 5 years (P < 0.004). The authors conclude that "Of the defined preoperative variables examined in this study, only one, contralateral carotid artery occlusion, was predictive of adverse perioperative events after CEA" (Reed et al., 2003).

Rockman et al., 2004

This retrospective review of a prospectively compiled database was performed to examine the impact of CAS on the management and outcome of recurrent stenosis. From a registry of patients treated for carotid disease, 105 procedures were performed from 1992 to 2002 for RCS and the data were divided into two time periods: through 1998, 77 reoperations before CAS was introduced at their institution and from 1999 through 2002, 12 reoperations and 16 CAS procedures performed for RCS. Perioperative stroke rates were higher in the later time period, but not significantly (7.2% vs. 5.2%, p = NS). Overall, the risk of perioperative stroke was the same for reoperation (5/89) and CAS (1/16) (5.6% vs. 6.3%, p = NS). Although not statistically significant, there was a trend toward a higher risk of perioperative stroke for patients treated with reoperation during the latter time period (8.3% vs. 5.2%, p = NS). They suggest that during later time period, CAS was most likely to be used in asymptomatic patients (68.6% vs. 41.7%, p = NS) with early (<3 years) RCS (87.5% vs. 41.7%, p= 0.01). They conclude, "Contrary to suggestions that CAS might improve the management of RCS, a review of our data shows the overall risk of periprocedural stroke to be no better since CAS has become available. The bias for using CAS for asymptomatic myointimal hyperplastic lesions, and reoperation for frequently symptomatic late recurrent atherosclerotic disease, makes direct comparisons of the two techniques for treating RCS difficult. It is expected that the overall risk for redo carotid surgery will increase, as fewer low-risk patients will be receiving open procedures. However, the increased risk among symptomatic patients undergoing reoperation suggests that endovascular techniques should be investigated among this group of cases as well."

Hill et al., 1999

Hill (1999) reported that re-do CEAs could be safely performed with a minimum of morbidity and mortality, and in their series of 390 carotid operations, procedure-related stroke-death rate was 0.8%. There were no differences between the stroke-death rates after primary CEA (N = 350, 42% asymptomatic) and reoperation (N = 40, 50% asymptomatic), and there were no postoperative deaths, strokes or permanent cranial nerve deficits in patients operated for recurrent stenosis. They postulated that early restenosis [< 24 months] is associated with myointimal hyperplasia and that late restenosis is related more to the development or progression of atheromatous plaque.

Jain et al., 2007

Jain and colleagues reported a retrospective review of 80 patients (46 male; mean age 64.1 years) with asymptomatic > 80% recurrent carotid stenosis (N = 49) or symptomatic > 80% stenosis (N = 32) who underwent a total of 83 reoperations under general anesthesia in a single community hospital setting between March 1988 and May 2005. The initial CEA used primary closure in 60 patients and prosthetic patch in 23. Results showed mean recurrence at 23.3 months in 33 patients with myointimal hyperplasia, 105.4 months in 29 with recurrent atherosclerosis, and 61.4 months in 19 with both hyperplasia and atherosclerosis. No perioperative strokes or deaths occurred, but one patient died from cardiac complications following combined reoperative CEA and coronary artery bypass grafting. Operative morbidity included reversible nerve injury (N = 5) and irreversible recurrent laryngeal nerve injury (N = 1). During follow-up of 3-153 months (mean 50.9 months) carotid occlusion resulted in one mild ipsilateral stroke and one non-hemispheric stroke. Eight patients required reoperation (mean 53.4 months), seven of whom were hypertensive. Long term follow-up at 153 months (12.75 years) showed 98.67% hemispheric stroke free rate and 95.85% all-stroke free rate. Patients on statins (P = 0.0042) and combined statin and aspirin (P = 0.032) had significantly increased interval between primary and secondary operation, and increased age correlated with decreased time to reoperation (P < 0.0001). The authors concluded reoperative CEA using standard vascular techniques was safe, effective and durable to prevent strokes in long term follow-up, that reoperative CEA should remain the mainstay of treatment when secondary intervention is required, and that statins had salutary effect on procedural durability (Jain et al., 2007).

Corriere et al., 2008

Corriere and colleagues reported a single-center, retrospective review of 259 patients (99.3% male) who underwent a total of 279 consecutive CEAs between January 1999 and August 2004 to determine the proportion of CEA patients who would be categorized as high risk by current criteria, characterize their preoperative angiograms, and determine potential technical challenges of CAS. Mean patient age was 68.3 ± 9.2 years (range 46-86), and 22 patients (7.9%) were > 80 years of age. The indication for CEA was asymptomatic stenosis in 159 patients (57%). Of the remaining 120 symptomatic patients, 34.8% had transient ischemic symptoms and 8.2% had permanent stroke as their respective indications for CEA. Four CEAs (1.4%) were performed for recurrent stenosis, 2 (0.7%) for neck irradiation or dissection, and 2 (0.7%) for contralateral laryngeal nerve injury. Published guidelines defining high risk for CEA were applied, and preoperative angiograms were examined for technical limitations to CAS. Of the 279 CEAs performed, 99 (35.5%) would have met one or more high -risk criteria, including 20 patients (7.2%) who had multiple high-risk criteria. Overall risks of perioperative stroke, MI and death were respectively 1%, 2.2% and 0.4%, for a combined major complication rate of 3.3%, but no major complication occurred in the 22 CEAs performed in patients > 80 years old. Of the 233 CEAs (83.5%) with preoperative angiograms available for review, the distribution of aortic arch configurations included types I (3.5%), IIa (39.5%), IIb (54.5%) and III (1.3%). Arch anomalies were observed in 35 patients (15.5%), and there were 171 patients (73.4%) with at least one angiographic finding that would have potentially increased technical difficulty of CAS. The authors noted that their observed frequency of adverse anatomic factors, while consistent with a prior report by Lin et al. (2005), was discordant with several reported high technical feasibility rates for CAS. Corriere and colleagues concluded that although a proportion (35%) of high risk CEA patients might be considered potential candidates for CAS, technically challenging factors based upon preoperative angiograms (some of which limit ability to perform CAS) are common and need to be anticipated when planning CAS (Corriere et al., 2008).

De Borst et al., 2008

De Borst and colleagues reviewed a consecutive series of 73 redo CEA procedures in 72 patients (57% male) with mean age of 66 years (range, 49-81 years). Mean interval between CEA and reoperation was 53 months (range, 8-192 months). Indications included symptomatic restenosis in 28 patients (38%), and patch angioplasty was performed in 62 patients (85%). Outcome measures included perioperative and late stroke and death, plus development of secondary restenosis. Results showed no perioperative deaths or strokes, and during mean follow-up of 52 months (range, 12-144 months) the Kaplan-Meier cumulative survival was 85% at five years. At five years, the cumulative rate of freedom from all strokes was 98% and freedom from ipsilateral stroke was 100%. After secondary procedures, re-recurrent stenosis > 50% occurred in 10 patients (13.7%) and cumulative freedom from re-restenosis (> 50%) was 85% at five years. Five patients (7%) received tertiary carotid reconstructions. The authors concluded that repeat CEA for recurrent stenosis could be performed safely with excellent long-term stroke protection (DeBorst et al., 2008).

4. MedCAC

No Medicare Evidence Development & Coverage Advisory Committee (MedCAC) was convened for this issue.

5. Clinical Guidelines

Screening for Carotid Artery Stenosis: An Update of the Evidence for the U.S. Preventive Services Task Force (USPSTF)

Pertinent to whether the general adult population should be screened for asymptomatic carotid stenosis, the USPSTF (December 2007) concluded that for individuals with asymptomatic carotid artery stenosis there is presently moderate certainty that benefits of carotid screening do not outweigh harms.[3] This "D" recommendation means the USPSTF recommends against the service and discourages screening for carotid stenosis in routine clinical practice.[4] The USPSTF noted that good evidence indicated that although stroke is a leading cause of death and disability, a relatively small proportion of all disabling, unheralded strokes is due to carotid artery stenosis. Regarding the benefits of detection and early intervention, the USPSTF found that good evidence indicated that in selected, high-risk trial participants with asymptomatic severe carotid stenosis, CEA by selected surgeons reduced the five year absolute incidence of all strokes or perioperative death by approximately 5%. Those benefits, however, would be less among asymptomatic people in the general population, and for the general primary care population, the benefits were judged to be no greater than small. In a supporting article in the *Annals of Internal Medicine*, the USPSTF reiterated that the proportion of all strokes attributable to previously asymptomatic carotid stenosis was low. Data sources included MEDLINE and Cochrane Library (January 1994 to April 2007), recent systematic reviews, reference lists of retrieved articles and suggestions from experts. Thirty day stroke and death rates from CEA varied from 2.7-4.7% in RCTs, and higher rates were reported in observational studies. Regarding limitations of the published literature, the USPSTF noted the body of evidence was inadequate to stratify people into categories of risk for clinically important carotid stenosis (Woolf et al., 2007).

6. Professional Society Position Statements

In addition to the public comments CMS received regarding the reconsideration request submitted by the ACC, SCAI, SVIN and SVM, CMS received a request from the Society for Vascular Surgery (SVS), on June 4, 2008, to mandate the use of national CAS registries for all CMS approved CAS facilities. In their letter, available via the tracking sheet for this reconsideration, the SVS states that they “are concerned that the CMS-required CAS data elements do not take full advantage of the meaningful opportunity brought about by the NCD mandate to report outcomes because those elements lack sufficient detail to perform a thorough risk-adjusted analysis.” The SVS recommends that CMS require “that national society registries serve as the CAS outcomes reporting mechanism, with simultaneous discontinuation of the current CMS CD-based data submission system.” The SVS also requests that “the reporting requirements be extended beyond the initial hospitalization to at least 30 days and potentially to 12 months since CAS procedures have event rates documented to occur after hospital discharge.” This additional request is addressed below in the analysis section of the decision memorandum.

7. Expert Opinion

Under “Controversies in Cardiovascular Medicine” in the October 2, 2007 issue of *Circulation*, thought leaders in the field debated the pros and cons of carotid stenting and ideal trial designs and investigations for future clinical trials.

Samuelson, et al. (2007) concluded:

> “Just as surgeons have learned over the years which patients should not be offered CEA, endovascular physicians are learning clinical and anatomic features that predict elevated risk for CAS. Therefore, endovascular physicians must rigorously apply the lessons learned in the CAS trials to avoid treating patients who are clearly at higher risk for complications with endovascular stenting. Patient-specific factors and individual clinician variability are critically important for outcome, but this is underemphasized among large randomized trials. A greater need exists to reduce morbidity and mortality by integrating CAS and CEA as complementary therapies while optimizing current medical treatments.”

> “Future trials should refine indications within a multimodality, comprehensive treatment protocol for groups of unselected patients. Evaluating treatment within these protocols will aim to improve patient outcomes overall, regardless of the specific treatments used. This paradigm more closely models the real clinical environment and is in line with the current NIH Roadmap for Interdisciplinary Research. The TACIT trial may be a step in this direction by clarifying outcomes between revascularization and modern best medical therapy [BMT]….” (Samuelson et al., 2007).

And LoGerfo (2007), concluded:

> “…no valid data are available on which to justify the use of stents in symptomatic patients from either the SAPPHIRE or ARCHeR trial. For asymptomatic patients, it is easy to suggest that a group of patients exists who are at such high risk for surgery that CAS is justified for stroke prevention. However, the immediate question then is whether such frail patients are better off with no intervention and modern drug management with platelet inhibitors and statins. CAS is not innocuous and has its own risk factors for periprocedural hemodynamic complications, stroke, and death… The statement that CAS provides the opportunity for stroke prevention for patients who are too high a risk for CEA has no foundation; in fact, under these circumstances, there is reason to be concerned that CAS is harmful compared with medical therapy alone.”

> “The bottom line here is that we need well-conducted, scientifically designed randomized trials to get answers about CASs. SAPPHIRE represents a failed opportunity. The only existing randomized trial in this country is the Carotid Revascularization Endarterectomy Versus Stent Trial (CREST), a National Institutes of Health-sponsored trial that began long before SAPPHIRE but is moving comparatively slowly now that the FDA has approved CAS and CAS registries” (LoGerfo 2007).

8. Public Comments

During the initial 30-day public comment period, CMS received 88 comments. Most commenters express support for an expansion of coverage, although the patient population to which an expansion of coverage should apply and the conditions under which expansion should occur is not widely agreed upon. Citations referenced by commenters not specifically addressed in this decision memorandum were determined to be outside the scope of this reconsideration because they have been reviewed in prior decision memoranda, address patient populations not included in this reconsideration or include no relevant data. A complete list of citations referenced by the commenters is provided in the appendices.

Comments with Evidence

Need for Coverage/Treatment Options

Yadav et al., 2004

One commenter cites the SAPPHIRE study results to stress the need for treatment options for patients who are at high risk for CEA due to anatomic risk factors. This commenter notes that the study shows higher event rates for patients with anatomic risk factors who undergo CEA than for those who undergo CAS. Therefore, treatment of patients with anatomic risk factors via CAS is more suitable than treatment with CEA. Another commenter notes that the relative risk of death, MI and stroke at 30 days was about 50% less among patients randomized to CAS vs. those randomized to CEA. Therefore this data supports at least equal coverage of asymptomatic patients for CAS and CEA.

Das et al., 1985; Meyer et al., 1994

Two commenters reference results from these studies to stress the importance of providing access to CAS for patients with anatomic high risk factors and subsequently the need for expanded coverage. These commenters specifically point to the high rate of complications, including stroke and death, that patients experience after undergoing repeat CEA.

Gasecki et al., 1995

Two commenters cite results from NASCET to highlight the need for expanded coverage and beneficiary access due to high stroke and death rates in patients with contralateral occlusion of the internal carotid arteries following CEA.

Mozes et al., 2004; Stoner et al., 2006

One commenter cites these studies to note the increased incidence of adverse events in patients who have anatomic risk factors and undergo CEA in support of expanding coverage of CAS.

Yadav et al., 2004; ARCHeR Trial; White et al., 2006; CABERNET Trial; SECURITY Trial; ACAS 1995; Barnett et al., 1991; Halliday et al., 2004

One commenter references these landmark studies which determined that the exclusion of patients with anatomic and physiologic high risk factors from receiving CEA was appropriate to support the need for expanded coverage of CAS.

AbuRahma et al., 2003; Nicolaides et al., 2005
One commenter stresses the importance of treatment options for patients with carotid artery stenosis as these studies identify significant risks of TIA and stroke in medically treated patients who are ineligible for CEA due to anatomic risk factors.

Barnett et al., 1998
One commenter cites this study to demonstrate the need for CAS as a treatment option in patients with anatomic risk factors who currently only have medical management as a treatment option.

ACAS, 1995
One commenter references the high risk of TIA and stroke associated with medical management as demonstrated through this study to stress the importance of providing treatment options to beneficiaries by expanding coverage of CAS.

Ballotta et al., 2003
One commenter cites this study which demonstrated higher morbidity in patients with severe medical comorbidities who underwent CEA to stress the danger of comorbid conditions in patients undergoing CEA.

Lepore et al., 2001; Ouriele et al., 2001
One commenter references these studies which confirm that NASCET-ineligible patients, most of whom were excluded due to a lack of technical suitability for CEA, are at high risk for CEA.

Appropriateness of Coverage
Roubin et al., 2006
One commenter notes that prospective registries show that patients with serious comorbid anatomic factors should be primary candidates for CAS.

Marine et al., 2006
One commenter references this single center, retrospective review which shows equivalent outcomes in patients treated with CAS and CEA despite the disadvantage CAS patients had due to the presence of anatomic high risk factors.

CAPTURE, CAPTURE 2, EXACT
Two commenters reference the 30-day stroke/death rates following CAS reported in these registry studies which are comparable in patients with and without anatomic high risk factors. The commenters assert that the similar outcomes demonstrate no elevated risk in CAS patients with anatomic risk factors and therefore support coverage of these patients.

CABERNET, BEACH subset analyses
One commenter contends that coverage should be expanded because the results of these studies indicate that patients with anatomic risk factors for CEA who undergo CAS have adverse event rates approaching or lower than the American Heart Association (AHA) benchmarks of 30-day stroke and death rates of 3% for asymptomatic patients and 6% for symptomatic patients.

Katzen et al., 2007; Gurm et al., 2008; CASES-PMS 30-day data; Yadav, 2006; CASES-PMS preliminary 1 year data
One commenter references these studies and reports to illustrate the established durability and generalizability of CAS in appropriate patient subgroups which merits coverage.

Gray, 2007
One commenter cites this presentation to support an expansion of coverage noting that 30-day all stroke and death rates reported from the CAPTURE 2 and EXACT registries approach or meet the AHA 30-day stroke/death benchmarks.

Dangas et al., 2001

Two commenters cite this single center study which showed CAS to have low complication rates in patients with anatomic high risk factors.

Al-Mubarak et al., 2002; Bianchi et al., 2007
One commenter cites these studies, which show low complication rates after CAS in patients with anatomic risk factors, to identify the benefit and safety of CAS in these patients.

Anatomic Risk Factors for CEA
Schneider et al., 2007
One commenter cites this study to assert that patients with hostile neck are best suited to CAS rather than CEA.

Landis et al., 2007; Narins and Illig, 2006
One commenter cites these studies which discuss and review anatomic factors that cause patients to be at high risk for CEA and the benefit of CAS over CEA for these patients.

Boules et al., 2005
One commenter references this study to identify recent MI and history of contralateral stroke as risk factors that increase the incidence of stroke, TIA and death within 30 days of undergoing CEA.

Gaspari et al., 2003; Hill et al., 1999; Illig et al., 2003; Jordan et al., 2002; Leseche et al., 2003; Mozes et al., 2004; Rockman et al., 2002; Stoner et al., 2005
Six commenters assert that results from centers of excellence indicate that anatomic risk factors including 1) previous CEA with recurrent stenosis; 2) prior radiation or radical surgery to ipsilateral neck; 3) surgically inaccessible lesion above C2; 4) contralateral vocal cord palsy; and 5) presence of tracheostomy stoma do not necessarily lead to increase surgical risk.

Reed et al., 2003; AbuRahma et al., 2000; Healy et al., 1989

Six commenters cite these series which demonstrate increased risk of stroke and death in patients with contralateral occlusion and increased risk of significant cranial nerve injuries which may be permanent with recurrent stenosis post CEA, respectively. However, these commenters note that these conclusions are not universally accepted.

Healy et al., 1989
Six commenters cite this study which found no increased risk of ipsilateral stroke in patients with recurrent stenosis post CEA as compared to patients without stenosis which suggests that patients with anatomic factors that increase surgical risk are not at increased risk for stroke due to their carotid stenosis.

CEA
Iyer et al., 2008
One commenter asserts that this article, in which the authors conclude noninferiority of CAS to CEA, based the CEA comparison group on flawed literature that resulted in a higher 30-day stroke/death rate than recent population based reports document.

Brahmanandam et al., 2008; Ringleb et al., 2008
One commenter notes that these meta-analyses conclude that CAS is associated with higher 30-day risk of stroke/death than CEA.

Sidawy et al., 2008 [abstract]
One commenter cites this abstract which provides an analysis of SVS Vascular Registry results that demonstrates better outcomes following CEA vs. CAS. CAS outcomes as identified in this analysis are similar to those demonstrated in CAPTURE, CAPTURE 2, EXACT and BEACH studies.

Coverage of Octogenarians
Chaturvedi et al., 2008 [abstract]

One commenter references lead in data from the CREST trial which demonstrates high stroke and death rates in octogenarians undergoing CAS and the CAPTURE registry which demonstrates a stroke rate of 7.2% in octogenarians and thus a marked procedural risk associated with CAS in this patient group. This commenter contends that CMS should rescind coverage for octogenarians due to increased risk of stroke and death.

Comments without Evidence

Coverage

Thirty three commenters support an expansion of coverage to patients with defined anatomic risk factors with symptomatic carotid artery stenosis between 50 and 69% and asymptomatic carotid artery stenosis $\geq$ 80%. Three commenters contend that coverage should be expanded for all high surgical risk patients with asymptomatic stenosis $\geq$ 80% and symptomatic stenosis $\geq$ 50%. Six commenters assert that coverage should be extended to patients with anatomic high risk factors and one commenter calls for an expansion of coverage to patients with non-anatomic high risk factors.

One commenter states that coverage should be expanded to symptomatic and asymptomatic patients at low risk for CEA, another commenter contends that low risk patients should be covered in registries and one commenter asserts that coverage should not be limited due to high surgical risk criteria, but rather CAS in patients at low, normal and high risk for CEA should be covered. One commenter contends that all FDA approved labeled indications for CAS should be covered.

Six commenters assert that coverage should be extended for asymptomatic patients with anatomic risk factors and $\geq$ 80% stenosis, while five commenters support coverage for this patient population only if unpublished outcomes are confirmed and six commenters support such an expansion of coverage only if facilities are required to participate in a multispecialty accreditation program and meet national benchmarks for CAS. Six commenters support an expansion of coverage. Two commenters support an expansion of coverage because multiple specialty societies agree with an expansion.

Six commenters support coverage of CAS without the use of an embolic protection device if the procedure is safe and the use of an EPD is not technically feasible. Two commenters assert that CMS should pay for CAS and CEA in the same patient populations.

Six commenters contend that coverage should not be expanded to patients with anatomic risk factors who have 50 – 69% stenosis. Eleven commenters do not support an expansion of coverage.

Evidence

Twelve commenters contend that available data supports an expansion of coverage while seven commenters assert that there is not enough data available to support an expansion of coverage and four commenters contend that available data does not support additional coverage. Two commenters contend that CAS is non-inferior to CEA and one commenter asserts that more data is needed on all treatment options (medical therapy, CEA and CAS). One commenter supports coverage due to FDA's approval of CAS based on level 1 evidence that underwent a well defined and detailed approval process which validates the safety and effectiveness of CAS procedures.

Anatomic Risk Factors

Four commenters agree with the 10 factors identified by the requestors of this reconsideration as anatomic factors that cause patients to be at high risk for CEA. These are defined as 1) previous CEA with recurrent stenosis; 2) prior radiation therapy to neck; 3) previous ablative neck surgery (e.g., radical neck dissection, laryngectomy); 4) surgically inaccessible carotid lesion, located above C2; 5) common carotid artery lesion below the clavicle; 6) contralateral vocal cord palsy; 7) presence of tracheostomy stoma; 8) contralateral internal carotid artery occlusion; 9) immobile neck; and 10) severe tandem lesions.

Another commenter identifies six factors that should constitute covered anatomic factors which include 1) previous CEA with recurrent stenosis; 2) prior ipsilateral radiation therapy to neck with permanent skin changes; 3) previous ablative neck surgery (radical neck dissection, laryngectomy, etc.); 4) common carotid artery stenosis below clavicle; 5) contralateral vocal cord paralysis; 6) presence of tracheostomy stoma. This commenter asserts that the other four anatomic factors identified by the requestors should not be considered high risk factors as data does not conclusively support their inclusion. This commenter also supports coverage of patients with TIA or minor stroke with 50-69% ipsilateral carotid stenosis and asymptomatic patients with 80-99% carotid stenosis who have one of the six anatomic factors listed above that establish high risk for CEA.

One commenter contends that anatomic factors should be defined as 1) previous CEA with recurrent stenosis; 2) prior radiation therapy or radical surgery to ipsilateral neck; 3) surgically inaccessible lesion above C2 or common carotid artery lesion below the clavicle; 4) contralateral vocal cord palsy; 5) presence of tracheostomy; and 6) contralateral internal common carotid artery occlusion. Another commenter contends that anatomic factors should include 1) prior neck radiation therapy; 2) ablative neck surgery; and 3) immobile neck. One commenter states that anatomic factors should include 1) previous CEA; 2) history of neck radiation; and 3) surgically inaccessible lesion.

Three commenters assert that the high surgical risk determination should be made by surgeons. One commenter contends that CMS should provide further guidance on the specific anatomic high risk factors.

Registries, Accreditation, Physician Qualifications

Three commenters assert that CMS should mandate the use of registries for CAS data collection. One commenter states that CMS should monitor CAS data. One commenter contends that CMS should require the use of a CAS facility accreditation program.

One commenter suggests that CMS establish more stringent credentialing requirements for physicians performing CAS. Another commenter states that physicians should be required to meet $\leq$ 3% 30 day post CAS stroke/death rate in asymptomatic patients. One commenter contends that surgeons with a stroke rate of > 2% in asymptomatic CEA patients should not be allowed to perform CEA.

Other Concerns
Two commenters stress the importance of expanding coverage to patients with anatomic high risk factors for CEA as CAS is the only treatment option for this patient group. One commenter asserts that the current coverage policy compromises patient care. One commenter expresses concerns regarding the liberal use of CAS. One commenter contends that outcomes should drive reimbursement for CAS. One commenter asserts that CMS should expedite this reconsideration process.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act §1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member” (§ 1862(a)(1)(A)).

The evidence base for carotid artery stenting continues to be of lower quality. There are a small number of randomized trials comparing CAS and CEA which have limited quality as we have discussed in prior decision memoranda. Acknowledging that existing case series and reviews may be markedly limited by selection bias, it is nonetheless informative in highlighting several other differences between procedures for carotid stenosis.

We were asked in this NCD request to consider expanding coverage to Medicare patients with carotid artery disease who are at increased risk of death or stroke and have anatomic factors that limit the use of CEA. We evaluated the proposed anatomic factors individually for their role as a contraindication to CEA and collectively to determine if evidence demonstrates that patients in the anatomic risk group meet the established outcome benchmarks according to symptomatic status.

The requestor submitted a letter with 3 references and an unpublished analysis of anatomic factors in support of their request. In reviewing the published evidence since our previous decision memorandum and the release of the 2007 BCBS TEC assessment, CMS found no comparative studies statistically powered to draw any conclusion regarding the impact of any intervention in patients with the requestors' group of anatomic factors upon patients' risk of stroke or death. BCBS noted limited evidence and a "clinical rationale" for the anatomic risk factors. CMS analyzed 15 observational studies and one industry-sponsored postmarket registry. In reviewing these studies, CMS focused broadly on unfavorable anatomic changes which are problematic for CEA but have evidence of beneficial and improved results with CAS.

Is the evidence sufficient to conclude that defined anatomic factors can be identified among patients with carotid stenosis that make carotid endarterectomy contraindicated?

We were asked to clarify which anatomic factors should be identified as high risk for CEA. The requestor asked that the following lesions be identified:

- Previous CEA with recurrent stenosis,
- Prior radiation therapy to neck,
- Previous ablative neck surgery (e.g., radical neck dissection, laryngectomy),
- Surgically inaccessible carotid lesion located above cervical vertebra C2,
- Common carotid artery lesion below the clavicle,
- Contralateral vocal cord palsy,
- Presence of tracheostomy stoma,
- Contralateral internal carotid artery occlusion,
- Immobile neck, and
- Severe tandem lesions.

In our 2005 decision, we included 3 anatomic factors in a list of significant comorbid conditions that may make persons poor candidates for CEA: contralateral carotid occlusion, previous CEA with recurrent stenosis and prior radiation treatment to the neck. We also allowed for the use of other anatomic factors that might have been used in prior CAS studies, basing this decision on the evidence available at that time. We reviewed available evidence on the exclusions from previous studies of CEA in that memorandum as well. In our 2007 decision memorandum, we referenced the high risk criteria cited by Bates et al., which added 4 anatomical criteria in their clinical expert consensus document: lesion at C-2 or higher, lesion below clavicle, contralateral laryngeal nerve palsy and tracheostoma. This paper was a consensus from clinical experts representing ACC, SCAI, SVMB, SIR and ASITN.

We found limited literature comparing outcomes of CEA or CAS in patients with the anatomic risk factors on the requestor's list and were unable to find a list generally accepted by all specialty societies. For some of the lesions, we found conflicting conclusions regarding the appropriateness and/or safety of performing CAS in these patients. We therefore asked for and received recommendations from numerous societies. The professional society commenters generally supported the inclusion of previous CEA with recurrent stenosis, prior radiation therapy to neck, previous radical surgery to the same side of the neck, contralateral vocal cord palsy, and presence of tracheostomy stoma as anatomic factors that lead to high surgical risk. However, there is not complete consensus on a complete list. Thus, we have determined that available evidence is not sufficient to definitively identify and designate anatomic factors that make CEA contraindicated in patients with such factors beyond those already identified in previous NCDs. The level of evidence and conclusions derived from this evidence do not clearly support or refute the benefit and/or safety and effectiveness of CAS or the danger of performing CEA in patients with these anatomic factors. Given the inconclusive evidence available, CMS proposes not to modify its current NCD discussion of anatomic risk factors.

Is the evidence sufficient to conclude that PTA with carotid artery stenting improves health outcomes for patients in whom CEA surgery is contraindicated due to anatomic factors with either (a) symptomatic carotid artery stenosis ≥ 50% or (b) asymptomatic carotid artery stenosis ≥ 80%?

The June 2007, BCBS technology assessment concluded that carotid artery angioplasty and stenting with or without EPDs for patients with carotid artery stenosis did not meet TEC criteria. The TEC noted that stroke/death rates following CAS surpassed those established as clinically acceptable and associated with overall net health benefit following CEA. While there was limited evidence and clinical rationale to suggest CAS may be beneficial in patients at increased anatomic risk (e.g., prior CEA, radiation therapy to neck, high lesion, spinal immobility, contralateral recurrent laryngeal nerve paralysis), the published evidence did not clearly differentiate outcomes for increased anatomic risk patients according to symptomatic status. BCBS TEC concluded there was insufficient evidence to draw conclusions regarding patients at increased anatomic risk.

There were several case series of carotid artery stenting in patients with one or more anatomical factors as well as analyses of post-approval studies according to the high risk factors. Treatment of carotid artery stenosis in patients with prior neck irradiation has been addressed by Protack and colleagues (2007) and Eskandari who found that CAS can be safely performed in this group in small case series. Protack found poor longer-term outcomes of CAS in this group and suggested that “these patients require closer postoperative surveillance and raise the question of whether CAS is appropriate for carotid occlusive lesions caused by radiation arteritis” (Protack et al., 2007).

The healthcare community has generally agreed that to be considered effective, procedures for carotid stenosis should have a periprocedural stroke/death rate of < 6% for symptomatic patients and < 3% for asymptomatic patients. These standards were developed for normal procedural risk patients. While there is dispute about the applicability of these values to patients who are at higher risk for CEA, CMS has used these criteria in previous decisions to evaluate carotid stenting outcomes. Higher procedure risk can occur from anatomical issues making surgery or stenting more risky or contraindicated, from medical comorbidities that increase the risk of death or stroke periprocedurally, or both. If the increased risk arises from an anatomical issue that makes CEA contraindicated, then one would expect that outcomes from CAS should not exceed the 3% and 6% outcomes referenced above.

For those patients who have anatomical contraindications to CEA, we examined data to determine whether CAS in that patient group would result in outcomes that equal or exceed the 3% and 6% standards. We initially looked for RCTs and published prospective studies that would provide a higher level of evidence, but there were no published RCT data on this subgroup. As discussed above, the published evidence we reviewed was not stratified by anatomic factors and symptomatic status and was of limited applicability to this question. While unpublished data was provided to CMS by the study sponsor of three post approval studies (Capture, Capture 2 and Exact), the Agency gives this evidence little weight in our review. In order for such evidence to have more weight in our review and analysis, it must be published in a peer-reviewed journal. The unpublished data submitted to CMS suggests that stroke and death outcomes in symptomatic and asymptomatic patients who are at high risk for CEA due to anatomic factors are approaching, and in some cases even lower than, the 6% and 3% benchmarks, respectively. However, the data provided did not consistently demonstrate outcomes meeting these benchmarks, nor did they sufficiently identify or address each anatomic factor separately.

CMS expects, based upon the trends demonstrated by the unpublished data provided, that outcomes for both symptomatic and asymptomatic patients at high risk for CEA due to anatomic factors will continue to improve. In order to consider expanding coverage to these patients, not only must outcomes be equal to or lower than the 6% and 3% benchmarks, but the data through which such outcomes are demonstrated should be published in a peer-reviewed journal. A peer-reviewed publication is an important element in the coverage determination process. It provides an opportunity for the public to review the study data and to consider our interpretation of the study results and conclusions based on the study results. CMS does not ordinarily base coverage determinations on unpublished evidence but will consider future expansions of this policy if additional adequate, peer-reviewed evidence is published.

CMS notes the comments of the Neurovascular Coalition (NVC) – comprised of the American Academy of Neurology (AAN), the American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS) Cerebrovascular Section, the American Society of Neuroradiology (ASNR), the Society of Interventional Radiology (SIR) and the Society of NeuroInterventional Surgery (SNIS) – which challenged use of non-peer reviewed and/or unpublished registry data as insufficient to support the expansion of coverage to the requestors' group of proposed anatomic factors.

In summary, while available evidence suggests the potential for improved health outcomes in patients who are at high risk for CEA due to anatomic factors, currently published data is not sufficient to expand coverage beyond the currently covered patient populations. Due to the lower quality and limited quantity of published, peer-reviewed evidence available addressing the patient populations under consideration, CMS has determined that an expansion of coverage is not reasonable and necessary and proposed to make no changes to the NCD.

Patients > 80 years of age

In our previous decision memoranda, we noted mounting evidence that the rate of death, stroke and MI after CAS is higher among patients who are ≥ 80 years of age compared with patients < 80 years. Lam et al. (2007), Sayeed et al. (2008), and Iyer et al. (2008) provide additional evidence that adverse outcomes in this age group are substantially higher. SVS advocated that CMS "rescind existing coverage for CAS in beneficiaries of age 80 years or older, and that CMS not extend coverage for asymptomatic patients or for symptomatic 50-69% stenosis patients if they are age 80 years or older." The consistency of these findings across the trials and studies, observed in both symptomatic and asymptomatic patients, creates concerns for the safety of older patients undergoing CAS. Although we have not and do not propose to restrict coverage according to age, we continue to have concern about proper patient selection to optimize outcomes.

Randomized Clinical Trials of CAS

Cognizant of the strengths and weaknesses of observational and experimental approaches, CMS believes in the importance of completing the ongoing RCTs and encourages future RCTs with medical therapy comparator arms. Such studies have the greatest potential for improving our knowledge about comparative therapies for carotid artery disease, and should provide scientifically valid evidence regarding the risks and benefits directly attributable to medical therapy with or without adjunctive surgical and endovascular interventions. This evidence is particularly needed to evaluate the treatment of patients not at high risk for CEA.

Registries

During our analysis, CMS received a supplemental request to mandate the use of formal CAS registries by all facilities approved by CMS to perform CAS. While we had hoped to address this request during this reconsideration period, we have determined that such a request must be addressed in a separate reconsideration of this policy.

Conclusion

As we concluded in our prior decision memorandum, “for CAS to be considered an alternative to CEA and improve health outcomes for asymptomatic patients with asymptomatic stenosis > 80%, the perioperative morbidity and mortality rates should be less than 3%.” For symptomatic patients with stenosis >50%, the benchmark is less than 6% death and stroke within 30 days of the procedure. The body of randomized trials and post approval studies does not demonstrate that CAS can be performed at that level. This is particularly concerning for asymptomatic patients since these patients do not have symptoms by definition and may be exposed to risks from the procedure. This continues to highlight the need for a randomized trial comparing CAS with optimal medical therapy. As a result of the inadequate peer-reviewed, published evidence, CMS has determined that expanding coverage is not reasonable and necessary and is proposing to make no changes to the NCD.

IX. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes to make no changes to the national coverage determination (NCD) for percutaneous transluminal angioplasty (PTA) of the carotid artery concurrent with stenting (Medicare NCD Manual 20.7).

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS normally divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Improved health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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Appendix C: Study Design

CMS recommends that RCTs or other clinical research studies enrolling Medicare patients specify and publish detailed description of the following:

- Study purpose and hypothesis;
- Inclusion and exclusion criteria fully describing the interventional and medical control arms;

- Use of (or investigation to establish, clarify or improve) standardized diagnostic criteria, uniform operational definitions and validated measurement techniques for patient selection, methods and outcomes;
- Use of blinded outcome assessors;
- Dates and explanations for all study protocol changes;
- Design phase and analytic strategies to minimize mixed effects of confounding and/or concurrent provision of other therapies or co-treatments;
- How adequate statistical power has been assured to enable drawing clinically meaningful conclusions regarding the study’s pre-specified primary and secondary endpoints;
- How results are to be generalized to the general Medicare population and affected Medicare subpopulations; and
- Method and timing for reporting of peer-reviewed preliminary results plus public release and publication of final research results to inform patients and providers about what has been learned.

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[1] Factors leading to increased anatomic risk in the BCBS TEC assessment are defined as prior CEA, radiation therapy to neck, high lesion, spinal immobility, and contralateral recurrent laryngeal nerve paralysis.

[2] http://www.bcbs.com/blueresources/tec/vols/22/22_01.pdf

[3] http://www.ahrq.gov/clinic/uspstf/uspsacas.htm

[4] http://www.ahrq.gov/clinic/uspstf/gradespost.htm#drecdrec

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